Zinc during and in convalescence from diarrhea has no demonstrable effect on subsequent morbidity and anthropometric status among infants <6 mo of age[1–4]

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ABSTRACT

Background: Preventing illness and improving growth in the first 6 mo of life is critical to reducing infant mortality. Zinc given for 14 d at the start of diarrhea has been shown to decrease the incidence and prevalence of diarrhea and pneumonia and improve growth in the 2–3 mo after, but no trial has been done in infants <6 mo of age.

Objective: This study sought to assess the effect of 14 d of zinc supplementation on subsequent morbidity and growth among infants 1–5 mo of age living in Pakistan, India, and Ethiopia.

Design: Infants with acute diarrhea were randomly assigned to receive zinc (10 mg/d; $n = 538$) or placebo ($n = 536$) for 2 wk. Weekly follow-up visits were conducted for 8 wk after the diarrhea episode. Incidence and prevalence of diarrhea and prevalence of respiratory infections including pneumonia were compared between the groups. Changes in weight, length, and corresponding z scores during the 8 wk of follow-up were also compared.

Results: One thousand seventy-four infants were enrolled at the start of follow-up. The groups did not differ significantly in the proportion of infants with at least one episode of diarrhea or respiratory infections. Infants who received zinc had more days of diarrhea (rate ratio = 1.20) than did the infants who received placebo. The groups had similar prevalences of pneumonia and overall respiratory infections. No significant differences in the mean changes in weight-for-age, length-for-age, and weight-for-length z scores were observed between the groups overall or in stratified analyses.

Conclusion: Young infants do not appear to benefit from 2 wk of zinc, unlike what has been observed among older children. *Am J Clin Nutr* 2007;85:887–94.

KEY WORDS Zinc, infants, growth, diarrhea management, pneumonia, diarrhea

INTRODUCTION

Diarrhea is the second leading cause of death among children <5 y of age, accounting for 18% of all child deaths (1). Although in recent decades the use of Oral Rehydration Solution has led to a decrease in the case fatality rate, diarrhea incidence rates have remained unchanged in the developing world (2). Malnutrition is an underlying risk factor for 61% of all childhood deaths associated with diarrhea (1). In addition to causing mortality, diarrhea is an important determinant of growth faltering in the developing world (3)

Zinc has been shown to be an effective treatment for diarrhea in young children, shortening the duration and severity of the diarrhea episode, and is now recommended by the World Health Organization (WHO) and UNICEF as part of diarrhea therapy for all children aged <5 y (4, 5). When given for 10–14 d during and after a diarrhea episode, zinc has benefits for the subsequent 2–3 mo in decreasing the prevalence of diarrhea [odds ratio (OR): 0.66, 95% CI: 0.52, 0.83] and the incidence of pneumonia (OR: 074; 95% CI: 0.40, 1.37) (6–10). Zinc for diarrhea treatment has also been shown to help children maintain their weight during a diarrhea episode and to improve growth in the weeks after an episode (11–13). The prevention of diarrhea and pneumonia is critical, especially in areas where limited access and financial constraints prevent prompt treatment, as is the case in much of the developing world (14, 15).

We conducted a randomized, placebo-controlled trial to assess the effect of zinc on diarrhea among infants 1–5 mo of age in Pakistan, India, and Ethiopia, where there are high rates of infant mortality, diarrhea, and stunting (16–19). We previously reported that there was no effect of zinc on the duration and severity of the treated diarrhea episode among these young infants (20). Herein we report the effect of zinc on morbidity and growth during 8 wk of follow-up after the index diarrhea episode. The current study is the first to assess the effects of zinc on subsequent morbidity and growth exclusively in infants <6 mo of age.

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SUBJECTS AND METHODS

We enrolled infants for this randomized, placebo-controlled diarrhea treatment trial and continued follow-up for 8 wk after the initial diarrhea episode to monitor subsequent morbidity and growth. Infants were enrolled from October 2003 through February 2005 from low income districts of Addis Ababa, Ethiopia, Karachi, Pakistan, and New Delhi, India. Complete screening and enrollment details have been described (20). Briefly, we enrolled 1110 infants 1–5 mo of age with <72 h of diarrhea who had no signs of other serious illnesses. Infants were excluded if they presented with a serious underlying illness, such as severe pneumonia or severe malnutrition, or if the infant required an overnight hospital stay. Sample size calculations for all outcome measures including morbidity and anthropometric follow-up were calculated with 80% power assuming a 2-sided α of 0.05. We enrolled 1110 infants to detect a difference of 0.16 in the length-for-age z (LAZ) score and a 25% decline in diarrhea incidence rate between zinc and placebo groups, assuming a 10% loss to follow-up.

The study was thoroughly explained to the parents or guardians of the eligible infants. The parents were told the purpose, potential benefits, potential risks, and time commitment for participation in the study. If the parent agreed, he or she was asked to sign a written parental permission document outlining the study details. All study methods, including consent procedures and documentation, were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board, the Addis Ababa Faculty of Medicine Ethics Board, the Aga Khan University Faculty of Science Ethical Review Committee, and the Society for Applied Studies Ethical Review Committee.

Infants who met all inclusion and no exclusion criteria and whose parent signed the permission document were enrolled in the study. Enrolled infants were randomly assigned to receive 10 mg zinc sulfate or placebo in the form of a dispersible tablet once per day for 14 d. Each blister pack was prenumbered according to a block randomization scheme conducted at the WHO in Geneva. Numbered packs were then sent to each study site. The randomization code was kept in Geneva until all analyses were complete. Zinc and placebo tablets looked and tasted the same to ensure blinding. All investigators, study personnel, and parents of enrolled infants were blinded from the randomization scheme until data analyses were complete.

A trained doctor or nurse conducted the baseline interview and clinic visit to assess the history of the diarrhea, breastfeeding status before and since the start of the diarrhea episode, and sociodemographic characteristics. Weight was measured by placing the lightly clothed infant on an infant scale and recording to the nearest 100 g The measurement was recorded after the needle was steady (in India and Ethiopia) or when the digital read display remained unchanged (in Pakistan) for several seconds. The scales were calibrated daily to ensure accuracy. Recumbent length was measured by using an infant length board and recording to the nearest 0.1 cm. All doctors, nurses, and data collectors were trained to measure both length and weight using standard methodology.

The infant was followed up at home or in the clinic every 3 d by a trained data collector until the infant passed <3 loose or watery stools/24 h and had maintained this non-diarrhea state for ≥48 h. On the last diarrhea episode follow-up visit the infant's length and weight were recorded as described above.

Weekly follow-up began 1 wk after the first diarrhea free day and continued for 8 wk. Daily information on morbidity was recorded. In the case where the parent or infant was unavailable or the visit fell on a holiday, the follow-up visit was conducted the following 1–2 d. Every effort was made to retain the infants in the study and find missing enrollees. Only if the infant was not found after daily visits for 7 d was the child dropped from the study. Until the end of the 14-d supplementation period, the data collector asked the mother about compliance with the tablets and verified each verbal report by counting the missing tablets from the blister pack. The data collector asked the mother about any diarrhea or respiratory symptoms during the previous 7 d and assessed the infant for current cough or difficulty breathing. If the infant had cough or difficulty breathing, the data collector counted the infant's respiratory rate, looked for chest indrawing, and took his or her axillary temperature. The data collector also asked the parent or guardian if the infant had had any other illnesses in the past week or had been to any health care facility for any reason. On the 4th and the 8th weeks of follow-up, the infant's length and weight were measured as described above. Infants were visited by the same data collector to ensure there was precision in the length and weight measures. Infants with observed or reported illnesses at the time of follow-up were referred to the study clinic or hospital for appropriate treatment.

Statistical methods

The sex of the infant, age, mean number of children in the household, mother's education, exclusive breastfeeding status, and presentation with cough or difficulty breathing in addition to diarrhea on enrollment were assessed by group for all infants. Differences in means were assessed with a Student's t test analysis and differences in proportion by Pearson's chi-square analysis.

An episode of diarrhea was defined as ≥1 d of diarrhea as reported by the caregiver. The episode was not considered over until there were >48 h with no reported diarrhea (21). The proportion of infants with ≥1 episode of diarrhea, the proportion of infants with ≥2 episodes of diarrhea, and the proportion of infants with ≥1 episode of dysentery during the 8 wk of follow-up were calculated.

The diarrhea incidence rate was calculated by dividing the total number of episodes of diarrhea per child by the total number of days of follow-up and multiplying by 30.42 for a monthly rate. Rate ratios (RRs) were then calculated.

Any infant was reported as having a respiratory infection during the past week if the mother reported any one or more of the following signs or symptoms: cough, fast breathing, difficulty breathing, chest indrawing, wheezing, nasal flaring, grunting, congestion, runny nose, or stuffed nose. Pneumonia was defined per the WHO definition (22), ie, as cough and difficult or fast breathing on the day of follow-up visit with a respiratory rate of ≥60 breaths/min for infants <2 mo of age or ≥50 breaths/min for infants aged ≥2 mo. Reported cases of pneumonia were considered respiratory infections and only classified as pneumonia if confirmed by an elevated respiratory rate on the day of follow-up. The proportion of infants with ≥1 reported respiratory infection and pneumonia episode were compared by group. The presence of any respiratory infection or pneumonia episode was recorded weekly. Prevalence of respiratory infection was calculated by finding the total number of weeks with respiratory symptoms, dividing by the number of weeks of follow-up, and

multiplying by 4.3. Prevalence of pneumonia infection was calculated by finding the total follow-up days where the child met previously described pneumonia criteria, dividing by the number of days of follow-up, and multiplying by 30.42. RRs were calculated.

Mothers were asked to report care-seeking at any health care facility, including a hospital, for each day during the 8 wk of follow-up. Hospitalization was defined as any overnight stay at a health care facility. The proportion of infants taken to a health facility and the proportion hospitalized during the 8 wk of follow-up were calculated for each group.

The proportions of infants with diarrhea, respiratory infection, or pneumonia were assessed by using a multivariate logistic regression, and a difference in rates was assessed with a robust Poisson regression. Before each full regression analyses for all outcome variables, interaction between supplementation group and nutritional status at the start of follow-up [weight-for-length *z* (WLZ) score] was assessed. Differences between the zinc and placebo groups for all proportions were determined by a multiple logistic regression analysis after adjustment for diarrhea episodes lasting >7 d, exclusive breastfeeding on enrollment, and the WLZ score at the start of follow-up.

The mean weight (g) and length (cm) at start of follow-up, week 4 of follow-up, and week 8 of follow-up were calculated and plotted by group. *t* Tests were used to calculate any differences between the zinc and placebo groups for both weight and length at all time points. *z* Scores were calculated by using the WHO reference population of breastfed infants (23). Whereas we previously used the National Center for Health Statistics/WHO reference population for the *z* score calculations, for this analysis, *z* scores were calculated by using the latest WHO recommendation (WHO Child Growth Standards/ANTHRO 2005), which calculates *z* scores on the basis of exact age and weight or length and compares to the WHO breastfed reference population (24). The mean weight-for-age (WAZ), LAZ, and WLZ scores were calculated at the start of follow-up and after 8 wk of follow-up and compared by group and site.

Baseline *z* scores were compared by the Student's *t* test analysis. The mean change in *z* scores (WAZ, LAZ, and WLZ) from the start of follow-up until the end of follow-up (week 8) was compared by group by using analysis of variance (ANOVA), with control for the baseline *z* score. The data were then stratified by baseline WAZ (<−2 WAZ compared with ≥−2 WAZ), LAZ (<−2 LAZ compared with ≥ −2 LAZ), breastfeeding status on enrollment (exclusive or not exclusive), and by sex. ANOVA regressions were used to assess differences between zinc and placebo groups for the overall mean change and for each stratified analysis while controlling for sex, WAZ, LAZ, exclusive breastfeeding, and the total days of diarrhea during the follow-up period. Possible interactions between site and treatment group were assessed for each outcome measure. Interaction terms were incorporated into the previously described, and no statistically significant differences were observed ($P > 0.20$) (results not presented). All analyses were performed by using STATA version 9.0 (Stata Corp, College Station, TX).

RESULTS

A total of 1074 infants began the weekly enrollment. Infants in the zinc group were more likely to be girls and to have been exclusively breastfed before the diarrhea episode than were infants who received placebo; all other characteristics were not statistically different between the 2 groups (**Table 1**). Of those enrolled, 998 infants completed the 8 wk of follow-up; 32 infants were not fully followed-up because they withdrew from the study. For 46 infants, the initial diarrhea episode lasted longer than 9 d; therefore, the follow-up weeks during that time were excluded. Infants in the zinc group contributed 4200 infant-weeks of observation and infants who received placebo contributed 4169 infant-weeks of observation for the morbidity analyses (**Figure 1**). One infant in the zinc group and 6 infants in the placebo group were missing final growth data and were therefore excluded from the growth analysis. Thus, 522 infants in the zinc group and 513 infants in the placebo group contributed complete data for the final growth analysis.

Both the proportion of infants with ≥one episode of diarrhea and the proportion of infants with ≥2 episodes of diarrhea were not statistically different between the groups (**Table 2**). No significant difference between the diarrhea incidence rates of infants in the zinc and placebo groups after control for covariates (RR = 1.02; 95% CI: −0.18, 0.15). Infants in the zinc group had more days of diarrhea during the follow-up period (RR = 1.22; 95% CI: −0.01, 0.36) after control for covariates.

The proportion of infants with ≥1 respiratory infections or pneumonia episodes was not significantly different between the groups (**Table 3**). The prevalence of respiratory infections (RR = 1.00; 95% CI: −0.09, 0.27) and the prevalence of pneumonia (RR = 1.04; 95% CI: −0.33, 0.49) were also not statistically different. No significant difference in the proportions of infants who were brought to a health care facility or hospitalized overnight at any point during follow-up was observed between the zinc- and placebo-supplemented infants (Table 3).

Weight and length were not significantly different between the zinc and placebo groups at the start of follow-up, week 4, and week 8 (**Table 4**). Mean weight and length increased linearly from the start of follow-up to week 4 and week 8. WAZ, LAZ, and WLZ scores at baseline were not significantly different between the zinc and placebo groups (**Table 5**). The average change in *z* scores per month were calculated for WAZ, LAZ, and WLZ scores. No significant differences in the monthly *z* score changes were observed between the zinc and placebo groups for WAZ, LAZ, or WLZ as assessed by ANOVA after control for covariates (Table 5). Also, no significant differences in the average change in WAZ, LAZ, or WLZ scores were observed when stratified by WAZ at the start of follow-up, LAZ at the start of follow-up, exclusive breastfeeding at enrollment, or sex (data not shown).

DISCUSSION

Zinc has been proven to be an effective treatment for diarrhea in children aged 6–59 mo and has been shown to decrease the incidence and prevalence of infectious diseases for 2–3 mo after 2 wk of daily zinc (4, 10, 25). However, there is uncertainty about the effect of this approach in young infants. We randomly assigned infants 1–5 mo of age with acute diarrhea to receive either zinc or placebo for 14 d and continued observations for 8 wk after the diarrhea episode. To our knowledge, the current study is the first to look at both the immediate and longer term effects of zinc on morbidity and growth among infants enrolled before 6 mo of

TABLE 1
Baseline characteristics by site and supplementation group[1]

	All sites		Pakistan		India		Ethiopia	
Selected baseline characteristics of infants in weekly follow-up	Zinc (n = 538)	Placebo (n = 536)	Zinc (n = 273)	Placebo (n = 270)	Zinc (n = 185)	Placebo (n = 183)	Zinc (n = 80)	Placebo (n = 83)
Boys (%)	49.1 (44.8, 53.4)[2,3]	56.7 (52.4, 61.0)	48.0 (43.9, 54.1)[3]	56.7 (50.5, 62.6)	45.4 (38.1, 52.9)	53.0 (45.5, 60.4)	61.3 (49.7, 71.9)	65.1 (53.8, 75.2)
Age at end of 3 d follow-up (mo)	3.4 ± 1.4[4]	3.4 ± 1.4	3.1 ± 1.3	3.1 ± 1.3	3.6 ± 1.5	3.6 ± 1.4	4.2 ± 1.4	4.2 ± 1.3
Children in household (no.)	1.9 ± 1.0	2.0 ± 1.0	2.2 ± 1.1	2.3 ± 1.1	1.7 ± 0.7	1.7 ± 0.7	1.4 ± 0.6	1.4 ± 0.6
Mother's education (no. of y of school completed)	3.7 ± 4.3	3.4 ± 4.2	1.8 ± 3.4	1.5 ± 3.1	5.1 ± 4.2	5.2 ± 4.3	6.6 ± 4.4	6.0 ± 4.5
Exclusive breastfeeding before the diarrhea episode (%)[5]	30.2 (26.4, 34.4)[3]	24.1 (20.5, 27.9)	47.6 (41.6, 53.7)[3]	38.1 (32.3, 44.2)	10.3 (6.3, 15.6)	9.3 (5.5, 14.5)	17.5 (9.9, 27.6)	10.8 (5.1, 19.6)
Children with cough or difficulty breathing (%)	34.2 (30.2, 38.4)	30.6 (26.7, 34.7)	30.4 (25.0, 36.2)	28.5 (23.2, 34.3)	41.1 (33.9, 48.5)	36.1 (29.1, 43.5)	31.3 (21.3, 42.6)	25.3 (16.4, 36.0)

[1] Differences in proportions were tested with Pearson's chi-square analysis, and differences in means were assessed with Student's t test.
[2] Mean; 95% CI in parentheses (all such values).
[3] Significantly different from placebo group, $P < 0.05$ (Pearson's chi-square analysis).
[4] $\bar{x}$ ± SD (all such values).
[5] Exclusive breastfeeding was defined as any infant who received only breast milk (no water) during the week before the diarrhea episode.

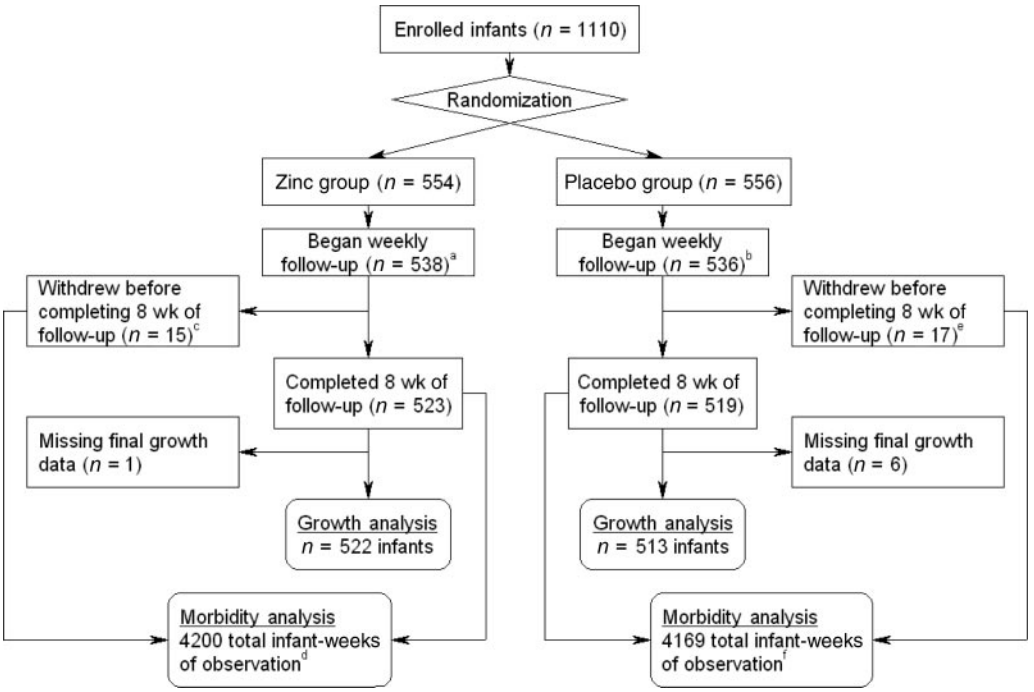

FIGURE 1. Flow diagram of the study. *a*) Reasons for loss to follow-up during the initial diarrhea episode: no longer wanted to participate ($n = 9$), moved from the study area ($n = 6$), or death ($n = 1$). *b*) Reasons for loss to follow-up during the initial diarrhea episode: no longer wanted to participate ($n = 8$), moved from study area ($n = 10$), hospitalized during diarrhea follow-up ($n = 1$), or death ($n = 1$). *c*) Reasons for loss to follow-up during weekly follow-up: no longer wanted to participate ($n = 1$) or moved from the study area ($n = 14$). *d*) Morbidity analyses included all infant weeks of observation. For the zinc group, 496 infants with complete follow-up contributed 8 full weeks of observation (3968 wk) and 28 infants with incomplete follow-up (withdrew early or index diarrhea episode lasted >9 d) contributed partial follow-up (232 total weeks of observation). *e*) Reasons for loss to follow-up during weekly follow-up: no longer wanted to participate ($n = 4$), moved from the study area ($n = 12$), or death ($n = 1$). *f*) Morbidity analyses included all infant weeks of observation. For the placebo group, 502 infants with complete follow-up contributed 8 full weeks of observation (4016 wk) and 18 infants with incomplete follow-up (withdrew early or index diarrhea episode lasted >9 d) contributed partial follow-up (153 total weeks of observation).

age. We previously reported that there was no effect of zinc supplementation for the treatment of diarrhea in this population of infants (20). Here we present the longer-term effects of zinc supplementation on infant morbidity and growth.

In our study, 14 d of zinc for the treatment of diarrhea in young infants did not decrease the incidence or prevalence of diarrhea episodes in the 8 wk after treatment. These results differ from the previously reported pooled analysis of short-course supplementation trials conducted in older children, which reported a 34% decrease in the prevalence of diarrhea among zinc-supplemented children when compared with those receiving placebo (10). It is difficult to explain why we observed a 20% increase in the prevalence of diarrhea in the zinc-supplemented infants; there is little biological plausibility for this. Our study observed no significant difference in the incidence of respiratory infections or pneumonia between the groups. Although a statistically significant positive effect of zinc on the incidence of pneumonia has only been observed in longer-duration supplementation trials, a positive trend has been observed among zinc-supplemented children in short-course trials as well (10).

TABLE 2
Incidence and prevalence of diarrhea by supplementation group

	Zinc ($n = 538$)	Placebo ($n = 536$)	P^1
Proportion of infants with ≥1 episode of any diarrhea (%)	59.5 (55.2, 64.7)[2]	58.8 (54.5, 63.0)	0.841
Proportion of infants with ≥2 episodes of any diarrhea (%)[3]	29.0 (25.2, 33.0)	36.4 (26.5, 34.5)	0.746
Proportion of infants with ≥1 episode of dysentery (%)[4]	3.5 (2.1, 5.5)	1.7 (0.1, 3.2)	0.049
Incidence of diarrhea (episodes/mo)	0.618 ± 0.683[5]	0.607 ± 0.697	0.810
Prevalence of diarrhea (d/mo)	2.68 ± 4.11	2.20 ± 3.19	0.030

[1] Differences in proportions were assessed by a logistic regression analysis after adjustment for original diarrhea episode lasting >7 d, exclusive breastfeeding upon enrollment, and weight-for-length *z* score at start of follow-up. Differences in rates were assessed by a robust Poisson regression after adjustment for original diarrhea episode lasting >7 d, exclusive breastfeeding, weight-for-length *z* score at start of follow-up, age, and sex.

[2] $\bar{x}$; 95% CI in parentheses (all such values).

[3] A new episode of diarrhea is defined as any day of diarrhea with ≥3 diarrhea-free days since the last diarrhea day of the last episode.

[4] Dysentery is defined as any day with blood in the stool.

[5] $\bar{x} \pm$ SD (all such values).

TABLE 3
Prevalence of respiratory illnesses and proportion of infants brought to a health facility by supplementation group

	Zinc (n = 538)	Placebo (n = 536)	P^1
Proportion of infants with ≥1 episode of respiratory infection (%)[2]	45.5 (41.3, 49.9)[3]	45.3 (41.1, 49.7)	0.448
Prevalence of respiratory infections (weekly episodes/mo)	0.681 ± 1.06[4]	0.680 ± 1.027	0.309
Proportion of infants with pneumonia (%)[5]	11.7 (9.1, 14.7)	9.7 (7.3, 12.5)	0.232
Prevalence of pneumonia (weekly episodes/mo)	0.07 ± 0.234	0.067 ± 0.242	0.702
Proportion who sought care at any health care facility (%)	39.4 (35.3, 43.7)	37.3 (33.2, 41.6)	0.239
Proportion of infants hospitalized (kept over night) at a health care facility (%)	1.9 (0.9, 3.4)	1.1 (0.4, 2.4)	0.148

[1] Differences in proportions were assessed by a logistic regression analysis with adjustment for original diarrhea episode lasting >7 d, exclusive breastfeeding upon enrollment, and weight-for-length z score at start of follow-up. Differences in rates were assessed by a robust Poisson regression after adjustment for original diarrhea episode lasting >7 d, exclusive breastfeeding, weight-for-length z score at start of follow-up, age, and sex.

[2] Respiratory infection is defined as any of the following symptoms: cough, fast breathing, difficulty breathing, chest indrawing, wheezing, nasal flaring, grunting, congestion, runny nose, or stuffed nose reported during the previous week

[3] Mean; 95% CI in parentheses (all such values).

[4] $\bar{x}$ ± SD (all such values).

[5] Pneumonia is defined as cough and difficult or fast breathing (respiratory rate ≥60 breaths/min for infants aged <2 mo or ≥50 breaths/min for infants aged ≥2 mo).

Additionally, no significant observed effect of zinc on growth was observed during the 2 mo after the diarrhea episode in these young infants. Of the 4 trials giving zinc for longer periods of time in this age group, 2 found limited effects on growth (26–29). One found a positive effect of zinc among infants with low serum zinc at the start of supplementation (29), and the other found a positive effect on weight during segments of the follow-up time but not overall (28). Zinc supplementation can be an important intervention to improve growth where dietary zinc intake among children is low and where high rates of stunting are present (30). In Ethiopia, Umeta et al (31) randomly assigned 100 stunted and 100 nonstunted infants 6–12 mo of age to receive zinc or placebo daily for 6 mo. Zinc supplementation increased the length of infants in both groups, but this was more pronounced among infants who were stunted at baseline. Although 27.8% of our enrolled infants were stunted at baseline, this is likely to reflect small size at birth in this young age group, rather than growth faltering as seen in later infancy. Throughout the follow-up period the infants in our study did not grow at an adequate rate to achieve optimal growth, which resulted in decreasing z scores. We observed greater growth faltering in length than in weight; stunting rates (<−2 LAZ) increased from 27.8% to 31.7% in 8 wk.

It is possible that the infants enrolled in the current study did not respond to the zinc with the benefits observed in other studies conducted in older children because they had not yet become zinc deficient. Nearly all these young infants were receiving breastmilk, which contains highly bioavailable zinc (32). Osendarp et al (29) supplemented Bangladeshi infants daily from 4–24 wk of age with 5 mg Zn or placebo and did not observe an effect on the incidence or prevalence of diarrhea or on the overall incidence of acute lower respiratory infections. However, when only zinc-deficient infants were assessed, there was a 70% decrease in the incidence of acute lower respiratory infections among infants who were supplemented with zinc compared with those who received placebo. A limitation of the current study was that we did not assess zinc status via serum zinc concentrations or the quantification of dietary zinc intake via breastmilk and complementary foods. For these reasons, we could not assess the variation in effect, if any, by baseline zinc status.

The exact mechanism by which zinc is an effective therapy for diarrhea and also prevents subsequent morbidity is not clearly known. One plausible mechanism is via the important role zinc plays in maintaining proper immune function and specifically enhancing cellular immunity (33). During the first year of life, the cellular immune system is still developing, thus the young infant may not respond to zinc in the same way as an older infant. Further investigation of the exact mechanisms by which zinc helps maintain immune function and prevents infectious diseases is needed to clarify why the positive effect of zinc is observed in older infants, but not in all infants under 6 mo of age.

TABLE 4
Mean weight and length at start, week 4, and week 8 of follow-up[1]

	Length			Weight		
Group	Start of follow-up	Week 4	Week 8	Start of follow-up	Week 4	Week 8
	cm			*kg*		
Zinc	58.53 ± 4.54	60.33 ± 4.46	61.99 ± 4.38	5.41 ± 1.28	5.94 ± 1.24	6.39 ± 1.20
Placebo	58.66 ± 4.26	60.42 ± 4.22	62.11 ± 4.20	5.34 ± 1.19	5.88 ± 1.16	6.33 ± 1.13

[1] All values are $\bar{x}$ ± SD.

TABLE 5
Baseline anthropometric status at the start of the weekly follow-up and mean change 8 wk after the supplementation period by supplementation group[1]

z scores	Zinc (n = 522)	Placebo (n = 513)
WAZ		
Start of follow-up	−1.27 ± 1.32	−1.41 ± 1.28
Change	0.11 ± 0.52	0.12 ± 0.60
LAZ		
Start of follow-up	−1.29 ± 1.28	−1.29 ± 1.35
Change	−0.19 ± 0.63	−0.19 ± 0.65
WLZ		
Start of follow-up	−0.31 ± 1.54	−0.51 ± 1.40
Change	0.25 ± 0.94	0.25 ± 0.97

[1] All values are $\bar{x}$ ± SD. WAZ, weight-for-age *z;* LAZ, length-for-age *z;* WLZ, weight-for-length *z*. Differences between zinc and placebo were assessed by using ANOVA with control for corresponding *z* score at start of follow-up, exclusive breastfeeding status, and total days of diarrhea during follow-up. No statistically significant differences were observed between the supplementation groups.

Because we previously reported no effect of zinc on the duration and severity of the diarrhea episode (20), it is not surprising that here we report no positive effect on morbidity or growth during the 8 wk of follow-up in the current study population. The only other study of zinc for diarrhea treatment in this age group also observed no effect of zinc on diarrhea duration, but had no follow-up assessment after recovery from illness (34). Additional research among specific subgroups of infants who appear to benefit from zinc supplementation, such as low-birth-weight and small-for-gestational-age infants, may help clarify current uncertainties and guide targeted zinc interventions.

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CLFW, REB, ZAB, and NB conceptualized the study. CLFW, ZAB, NB, TT, FS, and ST enrolled patients, implemented the study protocol, and provided ongoing monitoring. CLFW analyzed the data. CLFW wrote the manuscript. CLFW, REB, ZAB, and NB were responsible for editing the final manuscript. The expanded Zinc Study Group was also part of data collection, data management, and technical support for the duration of the study. The Zinc Study Group includes Shahid Rasool (Aga Khan University), S Qamaruddin Nizami (Aga Khan University), Temsunaro Rongsen (Society for Applied Studies), Vandna Suri (Society for Applied Studies), Sileshi Lulseged (Addis Ababa University), and Yeshewatsehaye Tesfaye (Addis Ababa University). The authors have no personal or financial conflicts of interests.

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